Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma

Supplementary Note and Supplementary Tables

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UK Biobank Supplementary Methods

Participant flow and variable derivation

Figures A and B present the participant flow for the cleaning and derivation of IOP and self-reported glaucoma variables.

Figure A: Flow chart for derivation of IOP outcome variable for UK Biobank GWAS.

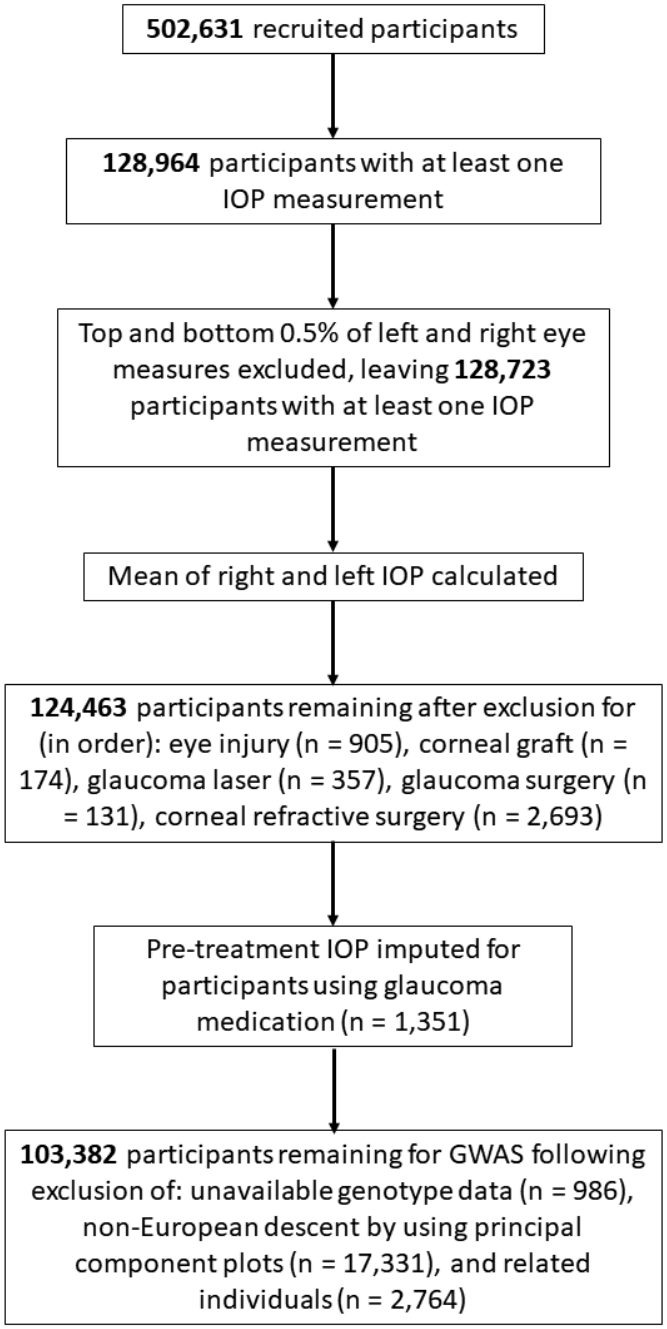
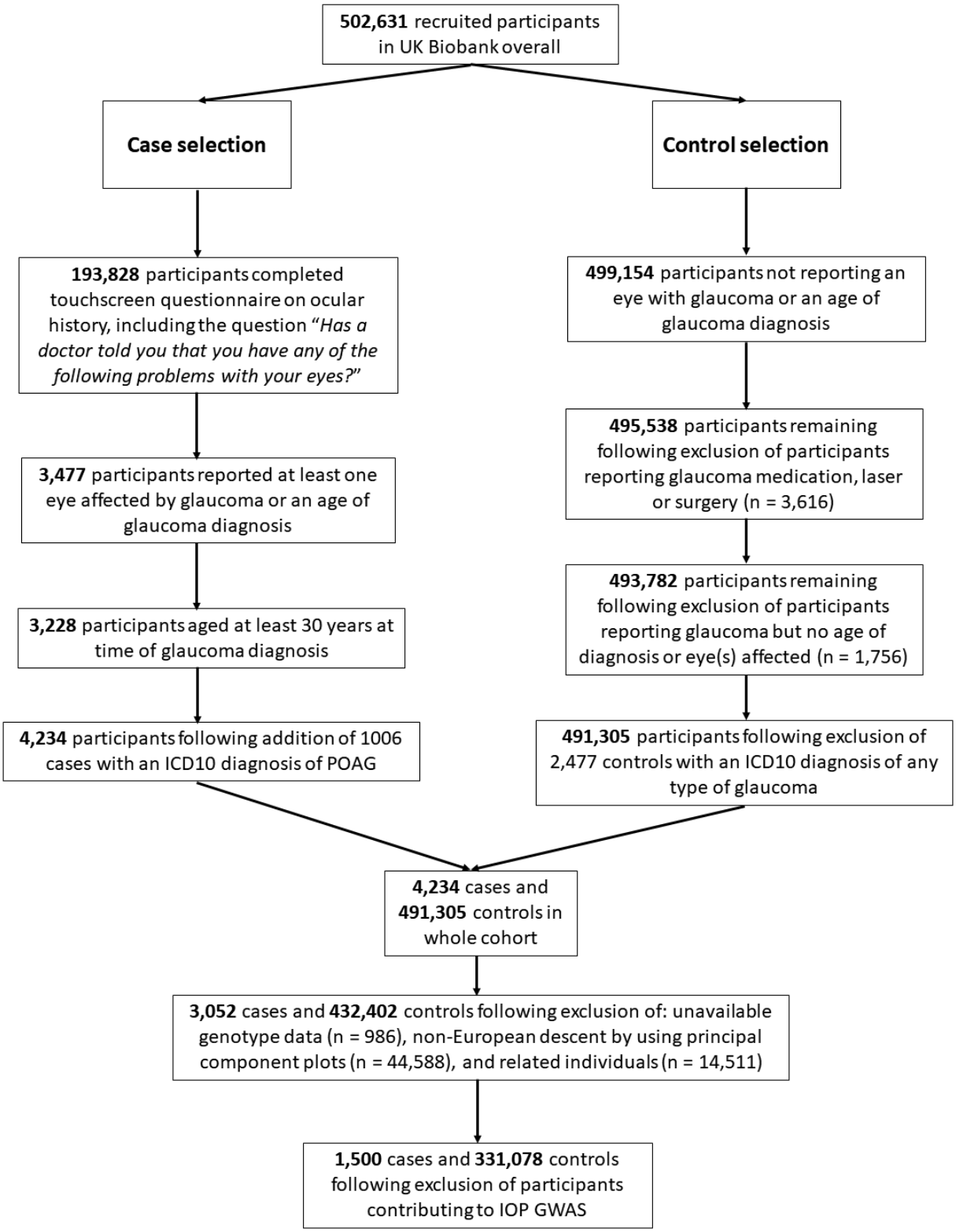


Figure B: Flow chart for derivation of self-reported glaucoma status in UK Biobank.



DNA extraction and genotyping

DNA extraction begun on buffy coat samples. DNA was extracted from 850 µl buffy coat (recovered from 9 ml of whole blood) on customised TECAN Freedom EVO® 200 platform (see URLs section). The samples were then processed in the approximate order received to produce genotype data. Genotyping was done using two arrays. The first array was the Affymetrix Axiom® platform with a custom-designed array described in the UK Biobank Axiom® Array Content Summary (see URLs section). Processing was done using a LIMS system to track instrumentation, Axiom consumables arrays and reagents and operators. The process is described elsewhere (see URLs section). Details on genotyping procedure and quality control can be found elsewhere (see URLs section). The second array is what was the UK BiLEVE, described elsewhere.[1]

Phasing on the autosomes was carried out using a modified version of the SHAPEIT2[2] program modified to allow for very large sample sizes. This new method (which we refer to as SHAPEIT3) modifies the SHAPEIT2 surrogate family approach to remove a quadratic complexity component of the algorithm.[3] In small sample sizes of a few thousand samples, this part of the algorithm, which involves calculating Hamming distances between current haplotypes estimates, contributes only a relatively small part to the computational cost. As sample sizes increase over 10,000 samples then this component becomes significant. The new algorithm uses a divisive clustering algorithm to identify clusters of haplotypes, and then calculates Hamming distances only between pairs of haplotypes within each cluster. Only haplotypes within each cluster are used as candidates for the surrogate family copying states in the HMM model.

A total of 806,466 directly genotyped DNA sequence variants were available after variant quality control. The UK Biobank team then performed imputation from a combined Haplotype Reference Consortium (HRC) and UK10K reference panel; phasing was performed using SHAPEIT3 and imputation was carried out via the IMPUTE4 program.[4] The variant-level quality control exclusion metrics applied to imputed data for GWAS included the following: call rate < 95%, Hardy–Weinberg equilibrium $P < 1 \times 10^{-6}$, posterior call probability < 0.9, imputation quality < 0.4, and MAF < 0.005. Sex chromosome and mitochondrial genetic data were excluded from this analysis. In total, 9,061,845 imputed DNA sequence variants were included in our analysis.

For sample quality control, we removed individuals with relatedness corresponding to third-degree relatives or closer, and an additional 480 samples with an excess of missing genotype calls or more heterozygosity than expected were excluded. In total, genotypes were available for 103,382 participants of European ancestry with IOP data**.**

It became apparent after commencing analyses that there were central problems with imputing SNPs not in the HRC panel. UK Biobank recommended filtering out these problem SNPs and we did this for all our analyses.

Association analysis covariables

The empirical association between IOP and other covariables is shown in the table below:

Variable	Beta (mmHg)	SE	*P*-value
Age	0.0610	0.0011	$<10^{-360}$
Sex	0.5189	0.0177	$1.8x10^{-187}$
PC1	-0.0081	0.0056	0.14
PC2	0.0103	0.0056	0.065
PC3	0.0004	0.0057	0.95
PC4	0.0048	0.0037	0.19
PC5	-0.0117	0.0015	$3.1x10^{-14}$

Since demographic factors and principal components had a small yet real effect over IOP, the above variables were included in the model.

EPIC-Norfolk Supplementary Methods

Genotyping and imputation

Initial genotyping on a small subset of EPIC-Norfolk was undertaken using the Affymetrix GeneChip Human Mapping 500K Array Set and 1,096 of these participants contributed to the IGGC meta-analysis.[5] Subsequently, the rest of the EPIC-Norfolk cohort were genotyped using the Affymetrix UK Biobank Axiom Array (the same array as used in UK Biobank); it is 6,595 of these participants (which includes no overlap with the 1,096 participants contributing to the IGGC meta-analysis[5]) that contributed to the EPIC-Norfolk IOP GWAS in the current study. SNP exclusion criteria included: call rate < 95%, abnormal cluster pattern on visual inspection, plate batch effect evident by significant variation in minor allele frequency, and/or Hardy-Weinberg equilibrium $P < 10^{-7}$. Sample exclusion criteria included: DishQC < 0.82 (poor fluorescence signal contrast), sex discordance, sample call rate < 97%, heterozygosity outliers (calculated separately for SNPs with minor allele frequency >1% and <1%), rare allele count outlier, and impossible identity-by-descent values. We removed individuals with relatedness corresponding to third-degree relatives or closer across all genotyped participants. Following these exclusions, there were no ethnic outliers. Data were pre-phased using SHAPEIT[2] version 2 and imputed to the Phase 3 build of the 1000 Genomes project[6] (October 2014) using IMPUTE[4] version 2.3.2.

Supplementary Note URLs

UK Biobank DNA extraction
http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/DNA-Extraction-at-UK-Biobank-October-2014.pdf.

UK Biobank Axiom® Array Content Summary
http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UK-Biobank-Axiom-Array-Content-Summary-2014.pdf.

UK Biobank Affymetrix genotype sample processing
http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583.

UK Biobank Phasing and Imputation Documentation
https://biobank.ctsu.ox.ac.uk/crystal/docs/impute_ukb_v1.pdf.

Supplementary Note References

1. Wain, L.V. *et al.* Novel insights into the genetics of smoking behaviour, lung function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic association study in UK Biobank. *Lancet Respir Med* **3**, 769-81 (2015).
2. Delaneau, O., Marchini, J. & Zagury, J.F. A linear complexity phasing method for thousands of genomes. *Nat Methods* **9**, 179-81 (2011).
3. O'Connell, J. *et al.* Haplotype estimation for biobank-scale data sets. *Nat Genet* **48**, 817-20 (2016).
4. Howie, B.N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* **5**, e1000529 (2009).
5. Springelkamp, H. *et al.* New insights into the genetics of primary open-angle glaucoma based on meta-analyses of intraocular pressure and optic disc characteristics. *Hum Mol Genet* **26**, 438-453 (2017).
6. Delaneau, O., Marchini, J., Genomes Project, C. & Genomes Project, C. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. *Nat Commun* **5**, 3934 (2014).

Supplementary Tables:

N.B. Supplementary Tables 2, 4, 6, 7, 8, 9, 10, 11 and 12 are in separate spreadsheet files.

Supplementary Table 1: Summary information for studies contributing to intraocular pressure (IOP) analysis. UK Biobank and EPIC-Norfolk analyses were carried out for the current study and previously unpublished. The International Glaucoma Genetics Consortium (IGGC) meta-analysis has been reported and we used publicly available results for the current study. EPIC – European Prospective Investigation of Cancer; BATS - Brisbane Adolescent Twins Study; BMES – Blue Mountains Eye Study; EPIC-I – first genotyping study on small proportion of cohort (these participants did not form part of the main EPIC-Norfolk replication cohort in the current study); ERF - Erasmus Rucphen Family; GHS - Gutenberg Health Study; ORCADES - Orkney Complex Disease Study; RS – Rotterdam Study.

Study	Geographic location	n	Mean age (SD)	Proportion women	Mean IOP (SD)	Genotyping chip	Imputation software	Imputation reference panel	Regression software
UK Biobank	Across UK	103,382	57.4 (7.8)	53.3%	16.1 (3.5)	Affymetrix UK Biobank Axiom Array and Applied Biosystems UK BiLEVE array	IMPUTE4	HRC and UK10K	BOLT-LMM
EPIC-Norfolk	Norfolk, UK	6,595	68.8 (8.0)	54.6%	16.8 (4.0)	Affymetrix UK Biobank Axiom Array	IMPUTE2	1000 Genomes phase 1, v3	SNPTEST v2.5
IGGC meta-analysis component studies (Springelkamp et al, *Hum Mol Genet* **26**, 438-453, 2017)									
BATS	Brisbane, Australia	1152	20.1 (4.0)	54.0%	15.8 (2.9)	Illumina HumanHap 610W Quad arrays (Illumina Inc., San Diego, CA, USA)	MACH	1000 Genomes phase 1, v3	Merlin
BMES	Blue Mountains, Australia	1769	64.0 (8.3)	56.8%	16.1 (2.7)	Illumina Human 660W Quad	IMPUTE2	1000 Genomes phase 1, v3	SNPTEST v2.5
EPIC-I	Norfolk, UK	1096	69.6 (7.9)	57.1%	16.4 (4.0)	Affymetrix GeneChip Human Mapping 500K	IMPUTE2	1000 Genomes phase 1, v3	SNPTEST v2.5
ERF	Rucphen, Netherlands	2589	49.1 (14.3)	55.0%	15.1 (3.0)	Illumina 6k; Illumina 318K; Illumina 370K; Affymetrix 250K	MACH	1000 Genomes phase 1, v3	ProbABEL
Framingham	Framingham, MA, USA	2771	54.7 (9.2)	55.0%	13.8 (3.5)	Affymetrix 250k_Nsp 250k_Sty HuGeneFocused50K	IMPUTE2	1000 Genomes phase 1, v3	GenABEL
GHS I	Mainz, Germany	2720	55.5 (10.8)	48.6%	14.2 (2.8)	Affymetrix Genome-Wide Human SNP 6.0 Array	MACH	1000 Genomes phase 1, v3	SNPTEST v2.5
GHS II	Mainz, Germany	1128	54.9 (10.8)	50.3%	13.9 (2.7)	Affymetrix Genome-Wide Human SNP 6.0 Array	MACH	1000 Genomes phase 1, v3	SNPTEST v2.5
ORCADES	Orkney, Scotland	1073	55.2 (14.2)	62.0%	15.0 (2.7)	IlluminaHumanHap300v2, HumanCNV370-Quad, Omni1, HumanOmniExpress- 12v1	IMPUTE2	1000 Genomes phase 1, v3	GenABEL
RAINE	Perth, Australia	1009	20.0 (0.43)	51.9%	15.4 (3.3)	Illumina 660W Quad Array	MACH	1000 Genomes phase 1, v3	ProbABEL
RS-I	Rotterdam, Netherlands	6010	69.2 (9.0)	59.7%	14.7 (3.2)	Illumina Infinium II HumanHap550 chip v3.0 array	MACH	1000 Genomes phase 1, v3	ProbABEL
RS-II	Rotterdam, Netherlands	2095	64.8 (7.9)	54.1%	14.2 (3.1)	HumanHap550 Duo Arrays + Human610-Quad Arrays Illumina	MACH	1000 Genomes phase 1, v3	ProbABEL
RS-III	Rotterdam, Netherlands	2992	57.2 (6.8)	56.3%	13.6 (2.9)	Human 610 Quad Arrays Illumina	MACH	1000 Genomes phase 1, v3	ProbABEL
TEST	Tasmania, Australia	663	25.6 (18.8)	60.5%	15.8 (3.1)	Illumina HumanHap 610W Quad arrays (Illumina Inc., San Diego, CA, USA)	MACH	1000 Genomes phase 1, v3	Merlin
TwinsUK	Across UK	2511	57.0 (11.6)	97.8%	15.6 (3.3)	Illumina 300K Duo and HumanHap610-Quad arrays	IMPUTE2	1000 Genomes phase 1, v3	GEMMA

Supplementary Table 3: Gene-set enrichment analyses results for IOP. *P*-values from the meta-analysis were used as an input. The analysis permutationally tested the observed versus expected number of gene scores above the 75th centile.

Database	Gene Set	Exp. Number genes above the 95%	Obs. Number genes above the 95%	GSEA *P*-value, 75% cutoff	GSEA FDR, 75% cutoff
Panther	Angiogenesis	4	15	7.30E-05	4.00E-03
GOTERM	collagen	1	6	4.00E-04	1.52E-01
GOTERM	basement membrane	3	8	4.00E-04	1.88E-01
KEGG	KEGG RENIN ANGIOTENSIN SYSTEM	1	1	4.00E-04	4.48E-02
PANTHER BIOLOGICAL PROCESS	Developmental processes	22	36	5.00E-04	1.15E-01
GOTERM	extracellular matrix structural constituent	3	10	6.00E-04	3.59E-01
Panther	Integrin signaling pathway	6	12	1.50E-03	9.50E-02
KEGG	KEGG FOCAL ADHESION	9	18	1.60E-03	1.51E-01
GOTERM	multicellular organismal development	39	55	1.90E-03	5.02E-01
GOTERM	signal transduction	71	89	1.90E-03	5.90E-01
GOTERM	cytoplasmic vesicle	10	16	2.00E-03	5.55E-01
GOTERM	neurotransmitter secretion	1	2	2.00E-03	3.41E-01
GOTERM	interspecies interaction between organisms	13	18	2.20E-03	4.87E-01
PANTHER MOLECULAR FUNCTION	Cell adhesion molecule	4	11	3.00E-03	4.58E-01
GOTERM	microtubule cytoskeleton organization	2	5	3.30E-03	6.03E-01
GOTERM	cell-cell adhesion	3	7	3.30E-03	4.78E-01
GOTERM	catecholamine metabolic process	0	1	3.40E-03	3.00E-01
PANTHER MOLECULAR FUNCTION	Other transcription factor	15	22	4.90E-03	5.48E-01
Panther	Dopamine receptor mediated signaling pathway	1	2	5.00E-03	8.05E-02
PANTHER MOLECULAR FUNCTION	Other signaling molecule	11	22	5.70E-03	3.71E-01

Supplementary Table 5: Genetic risk sharing between IOP and other phenotypic traits. The results shown are those from an LD Score regression of the IOP meta-analysis genome-wide significant results and all other publicly accessible (at the time of writing) GWAS summary statistics. Entries were sorted by significance (*P*-value) and only entries above a significance cutoff (P-value <0.05) are shown in this table. PMID = PubMed ID.

Trait correlating with IOP	PMID	Category	Ethnicity	Genetic Correlation r_g	SE	*P*
Heart rate	23583979	haemotological	Mixed	0.1428	0.0372	0.0001
Ever vs never smoked	20418890	Smoking behaviour	European	-0.1313	0.0413	0.0015
Sleep duration	27494321	sleeping	European	0.1171	0.0403	0.0037
FEV1/FVC	26635082	Lung function	European	0.1371	0.0488	0.0049
Sitting height ratio	25865494	anthropometric	European	0.1181	0.0484	0.0148
Mean platelet volume	22139419	haemotological	European	-0.0897	0.0389	0.0211
Total Cholesterol	20686565	lipids	European	0.068	0.0305	0.0257
Infant head circumference	22504419	anthropometric	European	-0.1335	0.0609	0.0285
Years of schooling 2016	27225129	education	European	0.0416	0.0199	0.037
Fasting glucose	22581228	glycemic	European	0.0865	0.0420	0.0393